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STUDIES ON ANTIMALARIAL DRUGS
THE METABOLISM OF QUININE
IN PREGNANT ANIMALS

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THE METABOLISM OF QUININE IN PREGNANT ANIMALS¹

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The use of quinine during pregnancy, either for the initiation of uterine contractions, or for the control of malaria, is not without danger to the fetus. There are several reports dealing with the toxic effects of quinine administered to induce labor (1-4). In those experiments the amount of quinine found in the fetus after such treatment was not determined because of the lack of a sufficiently sensitive and specific method. Investigations dealing with the placental transmission of quinine have been made on the human being (4, 5), rabbit (4), dog (5), and guinea pig (6). Although these experiments were chiefly qualitative, they demonstrated the ability of the placenta to transmit quinine to the fetus. In two instances, attempts were made to determine quantitatively the placental transmission of quinine (4, 5). In the human being, quinine passes through the placenta in the middle of the second trimester (5), but a quantitative determination of the capacity of the placenta to transmit quinine, in relation to the stage of pregnancy is lacking.

EXPERIMENTAL. The experiments reported here were designed to show the influence of pregnancy on the metabolism of quinine both in the maternal rabbit and in the fetus. The stage of pregnancy was accurately known from the mating date. In four rabbits, pregnancy was prolonged by the intravenous administration of 10 units of Gonadogen (Upjohn) on the 25th day of pregnancy. Quinine was given intravenously as a 1% solution of the hydrochloride in water. The dosages and analytical data are expressed in terms of the free alkaloid. In all experiments except those in which quinine was given by mouth, 10 mgm./kg. of quinine was given intravenously. The animal was sacrificed one hour later and samples taken for the determination of the quinine concentration. In one group of experiments, the time interval was varied.

Three fetuses of each litter were analysed separately except for the 12, 13 and 14 day stages in which all of the fetuses were combined for analysis. Earlier stages were too small for analysis. The organs from several fetuses were usually combined. In each case, three placenta were analysed, one intact and the other two separated into maternal and fetal portions. The maternal tissues were dissected as rapidly as possible, weighed and an aliquot dissolved in 2% NaOH. The quinine content was determined by the method of Kelsey and Geiling (7).

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² John J. Abel Fellow in Pharmacology. These studies are taken from a dissertation submitted to the University of Chicago in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June 1942.

RESULTS. *Quinine in the fetus.* The total quinine in the fetus determined one hour after administration to the maternal animal increased rapidly as pregnancy advanced, tending to parallel the increase in fetal weight. The concentration of quinine in the fetus was at the highest level on the 12 day (fig. 1), slowly dropped from the 12th to the 23rd day, and gradually increased from then until term. The concentration showed a marked fall in the post-term fetuses.

The concentration of quinine in tissues of fetuses older than 23 days was determined one hour after administration to the maternal animal. The liver ranged from 0.3 to 0.9, the kidney from 0.5 to 1.9 and the lung from 0.8 to 5.8 micrograms per gram. The quinine content of a full-term fetus was found to be 4.6 micrograms two hours after a single oral dose of 20 mgm./kg. After repeated daily oral doses of 20 mgm./kg. from the 21st day of pregnancy, a

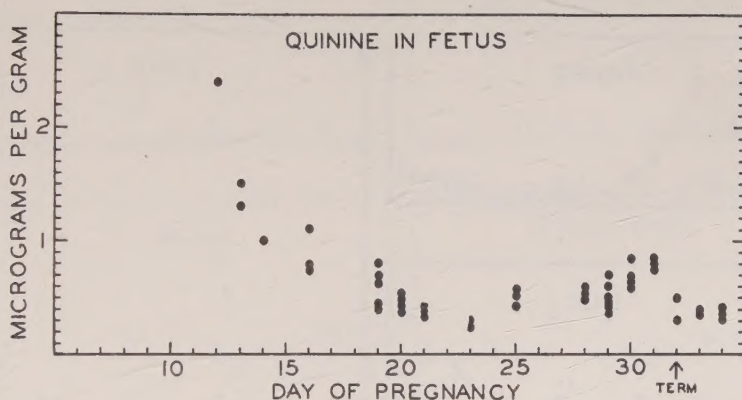


FIG. 1. QUININE CONCENTRATION IN THE FETUS ONE HOUR AFTER INTRAVENOUS ADMINISTRATION OF 10 MG. OF QUININE PER KILOGRAM TO THE MOTHER

Points from the fifteenth day to the thirty-fourth day represent individual fetuses; the others represent the average of each litter.

full-term fetus contained 8.9 micrograms of quinine two hours after the last dose. In another group of animals, the quinine was found to have practically disappeared from both the maternal and fetal tissues 12 hours after the injection of 10 mgm./kg. In four hours the concentrations were less than 10% of those observed 10 minutes after the injection.

The fetal portion of the placenta always contained more quinine than the maternal portion. The average of 15 fetal placentas was 6.9 micrograms total quinine, or a concentration of 3.1 micrograms per gram. For 15 maternal placentas the average values were 2.0 and 1.1 respectively.

Quinine in the maternal tissues. The relationship between the stage of pregnancy and the concentration of quinine in the tissues of the maternal animal one hour after injection are shown in figs. 2 and 3. Most of the tissues show the lowest values at the end of the second trimester, with rising values toward term. This is especially marked in the liver, spleen, blood, and lung. The tissue levels

observed in these experiments were always very low compared to levels found in similar experiments with dogs, cats and guinea pigs. The discrepancy was especially noticeable when values for liver quinine were compared. These

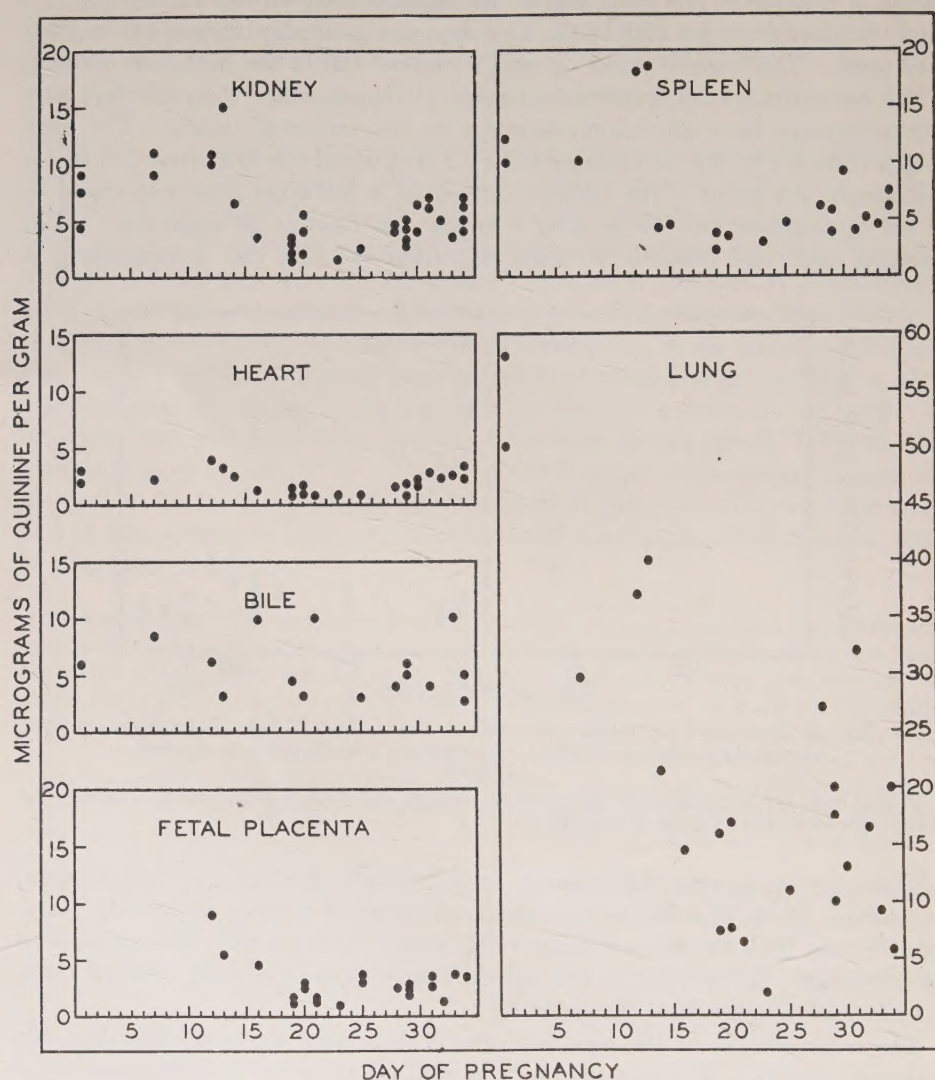


FIG. 2. QUININE CONCENTRATION IN MATERNAL ORGANS, BILE, AND FETAL PLACENTA OF THE RABBIT ONE HOUR AFTER THE INTRAVENOUS INJECTION OF 10 MG. PER KILOGRAM OF QUININE TO THE MOTHER

observations led to a study of the ability of the rabbit liver to destroy quinine *in vitro*, which will be reported in detail elsewhere (8, 9). These studies have shown the rabbit liver to be much more effective in destroying quinine than the liver of the cat, dog, guinea pig and several other species.

DISCUSSION. When standard experimental conditions are observed with respect to dosage, mode of administration, and the time interval following the administration of the quinine, there is a progressive increase in the quantity of

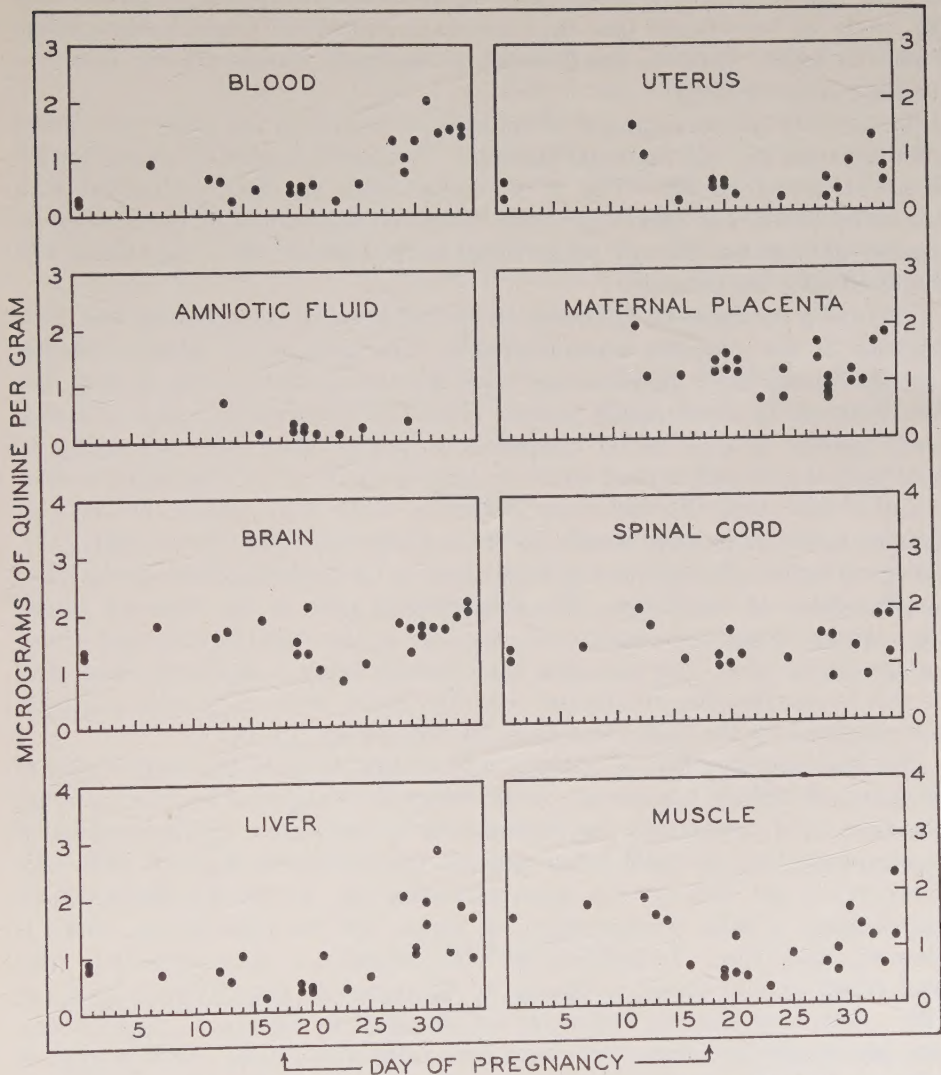


FIG. 3. QUININE CONCENTRATION IN MATERNAL ORGANS OF THE RABBIT ONE HOUR AFTER THE INTRAVENOUS ADMINISTRATION OF 10 MGm. PER KILOGRAM TO THE MOTHER

quinine passing from the maternal animal to the fetus as pregnancy progresses. This was found to be true for arsenic by Snyder and Speert (10), and for other substances (11, 12). In our experiments, prolonging pregnancy resulted in less quinine in the fetus than at term. Under similar conditions Snyder and Speert

(10) found more arsenic in the fetus after term. The fall in quinine concentration in the post-term fetus may be due to a decreased rate of transmission, to an increased destruction in the fetus or to excretion by the fetus to the maternal animal. Experiments *in vitro* suggest an increased destruction by fetal livers (8), while we have found that the placenta is capable of transmitting quinine from the fetus. Quinine was detected in maternal tissues shortly after its injection into the fetus.

At term the greatest amount of quinine was found in the fetus 10 minutes after injection into the maternal animals. Progressively smaller amounts were found at later intervals. This is in contrast with the results obtained with arsenic by Snyder and Speert (10); who found that the amount of arsenic traversing the placenta was directly proportional to the time at which the animal was sacrificed after the injection.

There is a considerable difference in the behavior of the maternal and fetal portions of the placenta toward quinine. The amount of quinine passing through the maternal placenta was twice as great as that passing through the fetal placenta in a ten minute period. The fetal placenta, although affording ready passage to considerable quantities of quinine, does have the ability to hold back or store within itself relatively large amounts of the alkaloid for a short period of time, thus affording some protection to the fetus against the alkaloid. Quinine is said to be fixed readily by the capillaries and held very loosely (13). This may explain the retention of large amounts by the fetal placenta which has an abundance of capillaries. The trophoblastic cells of the placenta, which have marked phagocytic power (14), may aid in this rapid fixation and transmission to the fetus. On the other hand arsenic, being a capillary poison, may be able to pass the placental barrier only after injury to the capillaries. Arsenic is firmly fixed by the tissues and excreted very slowly (15, 16).

The high concentration of quinine in the rabbit fetus in the early stages of pregnancy is difficult to explain. At this stage the fetal blood and the maternal blood are widely separated. In the final stage of pregnancy, the maternal blood is separated from the fetal blood only by an endothelial layer of cells (17). However, on the 12th day the tissue separating the two blood streams is fetal endothelium, strands of mesenchyme in places, and the plasmodium, which is often extremely thin. In addition, the fetal circulation is well established. The fetal vessels extend almost to the tips of the ingrowing trophoblastic folds and villi. Polymorphonuclear leucocytes are abundant in the venous plexus, vacuoles, and syncytium where these have been filled with blood. At this stage of pregnancy, the leucocytes and trophoblastic cells must be considered as playing a possible rôle in the transmission of the quinine.

After intravenous injection quinine was found in the highest concentration in the maternal lung, kidney and spleen, with the heart, bile, liver, muscle, brain, spinal cord, blood and uterus next in order. This organ distribution agrees in general with that reported by Lipkin (18). In the rabbit the lung initially fixed quinine in the greatest quantities. Lipkin reported only two analyses on rabbit

lungs and did not find the quinine content in them particularly high as compared with other organs. Hatcher and Weiss (13), studying quinine distribution in the cat, found that quinine is rapidly fixed by the capillaries, and that the lung, liver, kidney, and brain contained quinine in higher concentration than muscle or blood.

On the basis of quinine concentration, the ability of the liver to detoxify quinine is evidently greater in the non-pregnant animal and in the first and second trimesters of pregnancy than in the third trimester. In spite of the fact that the concentration of quinine rises to a higher level in the liver during the third trimester than at any time during the first two trimesters, the concentration of quinine did not increase as much in other organs as would be expected if the liver was the sole source of the enzymes responsible for the destruction of quinine.

The changes in the rate of quinine detoxication in the rabbit during pregnancy is of practical significance. That similar changes occur in the human is suggested by the work of Abe (19) on placental enzyme activity. In the human, toxic symptoms are less likely to occur during the second trimester. This is in accord with the increased detoxifying power occurring in the second trimester as seen in the rabbit with respect to quinine.

SUMMARY

Quinine readily passes the placenta of the rabbit and may be found in the fetus in highest concentration on the 12th day of pregnancy. It is rapidly destroyed or excreted and repeated daily doses show little tendency to accumulate in the fetus or maternal organs. The relatively high concentration in the fetal portion of the placenta suggests that some degree of protection is afforded by this organ.

The rabbit has a remarkable ability to destroy quinine, which is reflected by the very low concentrations found in the tissues shortly after intravenous injection. The stage of pregnancy has a distinct effect on the ability of the rabbit to destroy quinine. At the end of the second trimester, quinine is most rapidly destroyed, but at term there is more quinine stored in the tissues than in a non-pregnant animal.

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